BY HAND

International Preliminary Examining Authority
The European Patent Office
Erhardtstrasse 27
D-80331 Munich
Germany

15 February 2005

Dear Sirs

International Patent Application No.: PCT/GB2004/001663
George MARGETTS and Gavin Paul VINSON
Our Ref: N.88110A TAC/SLP/kle

We enclose a Demand for International Preliminary Examination of this application, electing all possible states, and a fee calculation sheet. Please debit all the relevant fees from our account No. 2805.0038.

We also enclose new page 22 showing claims 2 to 10 to replace previous claims 2 to 10. We request that International Preliminary Examination is carried out on the basis of the claims as amended. New page 22 has been amended under Article 34 PCT. Claims 2, 5 and 9 have been amended, as discussed below. Claims 3, 4, 6 to 8 and 10 remain unchanged.

Amendments

A typographical error has been amended in claim 2.

Claim 5 has been amended for reasons of clarity. Amended claim 5 has basis in the application as filed since each of the diseases mentioned in claim 5 is described as an angiotensin II related disease.

Claim 9 has been amended for reasons of clarity by removing the repetition of the word "atheroma" and by correcting the spelling of the word "nephropathy".

Clarity

We believe that claim 1 is clear since one skilled in the art would understand the meaning of the term "angiotensin II related disease". The Examiner is reminded that the clarity requirements of the EPO differ from those of other member states of the PCT and, if the clarity objection raised in the Written Opinion of the International Searching Authority is upheld, it is requested that the Examiner explain why the skilled person would not understand this term.

Novelty

The present invention concerns the use of trilostane and related compounds as defined in claim 1 to treat angiotensin II related diseases. The Examiner asserts that present claims 1-5, 7, 12, 13 and 18-21 lack novelty over D1. D1 however discusses the use of certain adrenal enzyme inhibitors, such as trilostane, in sustained release form, for inhibiting increased secretion of cortisol. Whilst D1 mentions insulin resistance and atherosclerosis, it only discusses these diseases in relation to increased cortisol levels. D1 does not discuss these diseases in the context of conditions whose cause is related to angiotensin II. Indeed, D1 does not discuss angiotensin II or diseases related to angiotensin II. D1 therefore does not disclose the use of trilostane or related compounds for treating angiotensin II related diseases. The present claims are therefore novel over D1.

Inventive Step

The Examiner argues that the present claims lack inventive step over a combination of D3 and D4. The Examiner states that D3 shows that an aldosterone blocker can be used to treat heart failure and that it would be obvious to use trilostane since that D4 shows that trilostane is an aldosterone blocker. The data illustrated in D4 was collected from adrenal cells *in vitro*. Trilostane treatment of smooth muscle cells *in vivo*, however, occurs without affecting circulating aldosterone levels. This is shown in Example 4 and Figure 3b of the present application. Thus, trilostane is not acting as an aldosterone blocker when used *in vivo* in this Example. Further evidence showing that the effect of trilostane is independent of aldosterone can be found in Examples 1 (Table 1), 2 (Table 2) and 3 (Fig 2). In Examples 1 and 2, each of the tests was carried out *in vitro* and in the absence of aldosterone. Example 3 is carried out in the presence of losartan, an angiotensin type 1 receptor blocker which would, in turn, block any possible residual aldosterone synthesis.

Thus, a skilled person starting from D3 would search for an aldosterone blocker. However, one skilled in the art would easily be able to determine that, *in vivo*, trilostane is not an aldosterone blocker. It would therefore not be obvious to use trilostane as an aldosterone blocker and subsequently one would not use trilostane for the applications described in D3.

None of the prior art documents discloses or teaches towards the use of trilostane or related compounds for the treatment of angiotensin II dependent conditions. We therefore submit that the

present claims are inventive.

Please acknowledge receipt of this letter by stamping and returning the acknowledgement copy provided.

Yours faithfully

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2. Use according to claim 1, wherein in formula (I) R_1 is hydrogen or methyl and/or R_2 is hydrogen or methyl and/or R_4 is hydroxy or R_3 and R_4 together are oxo and/or R_5 and R_6 are methyl.

3. Use according to claim 1, wherein the compound of formula (I) is trilostane, ketotrilostane or epostane.

4. Use according to any one of claims 1 to 3, wherein the angiotensin II related disease is a cardiovascular disease.

5. Use according to any one of the previous claims, wherein the angiotensin II related disease is congestive heart failure, post myocardial infarction, cardiomyopathy, diabetes, renal failure, metabolic syndrome (Syndrome X) or arrhythmia.

6. Use according to claim 4, wherein the cardiovascular disease is post myocardial infarction.

7. Use according to any one of the preceding claims, wherein the medicament is administered in an amount of from 0.5 to 4 mg/kg/day.

8. Use according to any one of claims 1 to 3, wherein the angiotensin II related disease is a proliferative disease.

9. Use according to claim 8, wherein the proliferative disease is peripheral arterial disease, cerebro vascular disease, cardiofibrosis, cardiac myopathy, diabetic retinopathy, diabetic gangrene, diabetic nephropathy, scleroderma, aneurism, asthma or atheroma.

10. Use according to claim 8 or claim 9, wherein the proliferative disease is cardiofibrosis.